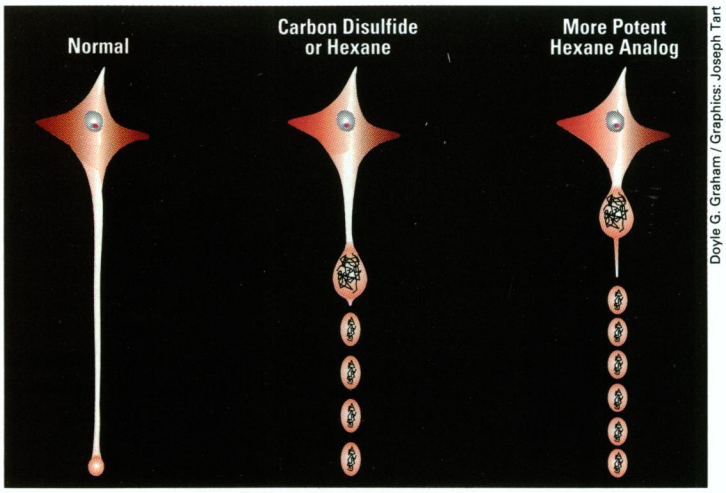
by the late Irving J. Selikoff of the Mount Sinai School of Medicine, was established in Carpi, Italy, to honor the birthplace of Bernardino Ramazzini, the founder of the science of occupational medicine.

At the conference, held October 29–31, data presented by Ronald Melnick of NIEHS highlighted inconsistencies and gaps in the hypothesis linking accumulation of $\alpha 2_u$-globulin, a protein synthesized in livers of male rats, and gasoline-induced carcinogenicity in the male rat kidney. Although the $\alpha 2_u$-globulin hypothesis explains some rat male kidney tumors caused by some chemicals, new data support the view that alternative mechanisms must be operating for gasoline. Cesare Maltoni and colleagues from the Institute of Oncology in Bologna reported that trimethylpentane produced testicular tumors but not kidney tumors in male rats after lifetime exposure. In long-term studies on the new gasoline additive methyl-*tert*-butyl ether (MTBE), significant increases in lymphomas and leukemias were observed in female rats, and testicular tumors were increased in male rats. Larry Andrews of ARCO chemical company also reported significant increases in kidney tumors and a borderline increase in testicular tumors in male rats and an increase in liver tumors in mice as a result of exposure to MTBE. The role of $\alpha 2_u$-globulin in the induction of kidney tumors by MTBE was seriously questioned, however, because $\alpha 2_u$-globulin was not detected in protein droplets present in the kidneys of male rats treated with MTBE.

The collegium reaffirmed its position that chrysotile asbestos is a cause of cancer, based on well-documented animal and human studies that have consistently demonstrated lung cancer and mesothelioma after exposure. No safe levels of exposure to any type of asbestos have been found. Yasunosuke Suzuki of the Mount Sinai School of Medicine pointed out that lung burden analyses are not satisfactory indicators of exposure or carcinogenic risk because chrysotile fibers can translocate from the lung to the mesothelium. To protect public health and prevent diseases caused by chrysotile, the collegium recommends that asbestos not be used in the future and be removed where appropriate.

In the session on pesticides and dioxin, Mary Wolff, also of the Mount Sinai School of Medicine, reported an association between blood levels of organochlorine residues and increased risk of breast cancer. Many of these environmental contaminants may cause adverse biological effects through estrogenlike activities. Ellen Silbergeld of the University of Maryland described the mechanistic link between receptor-mediated changes in gene expression and multiple toxic effects induced by dioxin. Pier Alberto Bertazzi of the University of Milan presented a 10-year follow-up of epidemiological data showing increases in several cancers resulting from the accidental release of dioxin in Seveso, Italy, in 1976.

The 1993 Ramazzini Award was presented to Suzuki for his contribution to the scientific knowledge on the pathology of mesotheliomas among asbestos-exposed workers. The proceedings of the conference will be published in a 1994 issue of the *Ramazzini Annals*.



Doyle G. Graham / Graphics: Joseph Tart

Killing the messengers. Carbon disulfide and hexane damage nerves by causing swellings of neurofilaments and degeneration of nerve axons.

Hexane and Carbon Disulfide

The solvents *n*-hexane and carbon disulfide are commonly used in industrial settings around the world. Although chemically different, both solvents can result in identical damage to the human nervous system characterized by the initial development of large swellings and subsequent degeneration of the distal axon, the part of the nerve that sends messages to other cells.

Under a grant from NIEHS, researchers Doyle Graham, Venkataraman Amaranth, and William Valentine of Duke University Medical Center, and Sally Pyke and Douglas Anthony of Harvard Medical School have detailed the mechanism by which these chemicals damage neurons. In the process, they have also identified a red blood cell protein that can serve as a biomarker for exposure.

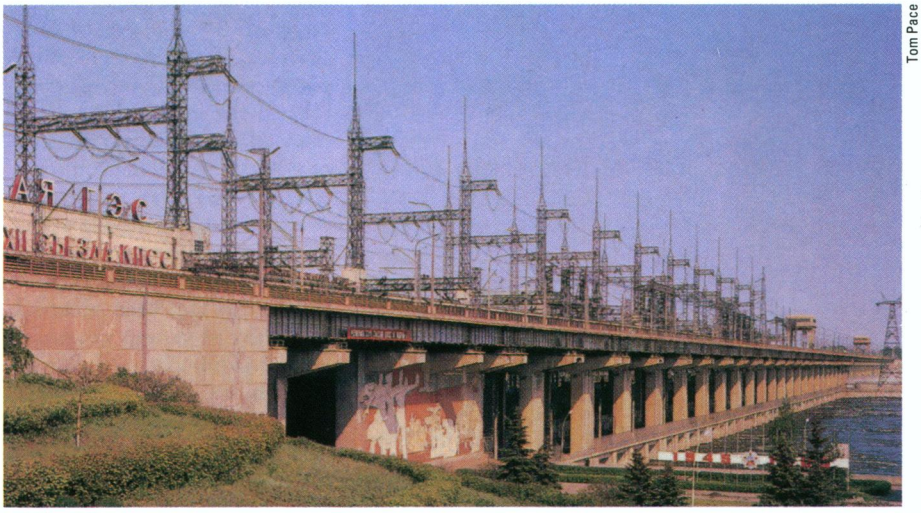
n-Hexane is used primarily as a glue solvent in the furniture and shoe industries. Before widespread knowledge of the danger of this chemical, facilities were often poorly ventilated, and workers inhaled the vapors throughout the workday. The neurotoxicity of *n*-hexane was initially discovered in 1964 among Japanese workers, and later among workers in Italy, Morocco, France, and the United States. Neurotoxicity has also been observed in youths in various countries who intentionally sniff glue to get high.

Carbon disulfide has been used since the early nineteenth century as a solvent in the manufacture of sulfur matches and in the extraction of fats. More recently, it was used in the cold vulcanization of rubber, and today it is used in converting cellulose into rayon fiber and cellophane.

The symptoms of hexane and carbon disulfide neurotoxicity are numbness of the toes and fingers, followed by loss of sensation in the feet and hands, loss of distal reflexes, and weakness of the intrinsic muscles of the feet and hands. Studies of peripheral nerve biopsies typically reveal paranodal axonal swellings, retraction of myelin, the fatty substance that sheaths nerve fibers, from cerain nodes, and degeneration of the distal axon. The axonal swellings have been shown by electron microscopy to contain disordered masses of neurofilaments. After exposure ceases, sensory and motor functions continue to decline for one to four months, followed by recovery. The degree of recovery is inversely related to the severity of the neuropathy, and is complete in mild cases.

Over the past 20 years, studies in a number of laboratories have revealed the sequence of molecular events that result in damage from *n*-hexane and carbon disulfide exposure. For both animal and human subjects, it has been observed that long axons are more vulnerable than short ones, reflecting the greater number of axonal targets for injury with each increment of axonal length.

n-Hexane is metabolized in the liver to γ-diketone, 2,5-hexanedione (HD)—its ultimate toxic metabolite. Early studies by Valentine and colleagues demonstrated intramolecular and intermolecular crosslinking of proteins after incubation with γ-diketones. Given the stability of neurofilaments in the axon and their slow rate of transport to the site of hydrolysis of proteins at the synapse where simpler, more soluble products are formed, researchers hypothesized that neurofilament crosslinking was the central, underlying event



Tom Pace

Scenic Volgograd. U.S. and Russian scientists are working to restore the air quality that industries along the Volga River destroyed.

leading to neurofilament-filled swellings.

Recently, Valentine and colleagues have shown that carbon disulfide also results in protein cross-linking, although by a different mechanism from *n*-hexane. The initial dithiocarbonate adduct formed on protein decomposes to isothiocyanate derivatives, which then react with protein nucleophiles (electron-donating reagents) to result in cross-linking.

During chronic intoxication with either hexane or carbon disulfide, covalent cross-linking of proteins in the axon is paralleled by cross-linking of spectrin, a red blood cell membrane protein. This finding suggests that exposed populations could be evaluated through periodic blood sampling, and the quantity of spectrin cross-linking could be used to identify people in danger of developing neurotoxicity.

In the United States and other industrialized nations, instances of damage from hexane and carbon disulfide exposure have almost disappeared thanks to protective measures in the workplace and substitution of other chemicals. Processes using either of these chemicals are typically sealed off and ventilated separately. Workers who occasionally work around these processes must wear respirators. Workers that have physical contact with products, such as rayon, that may contain small concentrations of hexane or carbon disulfide, wear protective clothing and gloves.

Both industry and labor groups have expressed interest in the recent findings. "We still have locals who use these chemicals, and any information as to how exposure leads to neuropathy can help us in training workers how to protect themselves," said Rich Uhlar, industrial hygienist with the International Chemical Workers Union. Uhlar said the ICWU is particularly interested in findings that might allow a simple blood test to be used as a biomarker of exposure.

John Stewart, president of Courtauld Fibers in Axis, Alabama, uses carbon disulfide in the manufacture of rayon in his plant. "Any information that would lead us to better understand how carbon disulfide is metabolized—particularly the reversibility of the condition—is of value to us," Stewart said.

Cleaner Air in Volgograd

There was a time when the city of Volgograd was a mecca for Russian citizens suffering from respiratory problems such as asthma. There, along the banks of the river they fondly called Mother Volga, Russians could find an ideal dry climate and clean air. But in the last several decades, the Volga River's character has changed: today, it is a highly polluted receptacle for industrial, agricultural, petrochemical, and radioactive wastes dumped along its 2300-mile stretch from the north of Moscow to the Caspian Sea.

In mid-1993, Volgograd was chosen as the test site for the initial phase of a four-year Russia Air Management Program (RAMP), a joint U.S. Agency for International Development (USAID)–EPA project working with the Russian Ministry of Environment and Nature Protection. Before deciding on Volgograd, a team of American and Russian scientists evaluated several other Russian industrial centers, including Lipetsk, Samara, and Nizhny Novgorod, but only Volgograd had such a large number of different kinds of polluters.

Long and narrow, the city of Volgograd stretches for 70 miles along the river's west bank a few hundred miles north of its delta. Clusters of heavy industry follow the city in a checkerboard pattern from north to south, including a steel mill and iron foundries, aluminum reduction and carbon black manufacturing plants, a caustic soda manufacturer, several chemical factories, a petroleum refinery, and large-equipment manufacturing facilities.

"It was this variety of sources that made us choose Volgograd," says Tom Pace, the EPA's program manager for RAMP, managed by the EPA Office of Air Quality Planning and Standards. "This way the city can be used as basically a palette, allowing the Russians to look at how they can deal with many different air pollution problems. It can give us a lot of flexibility."

RAMP is one of the first federal projects funded under the 1993 U.S. Freedom Support Act (FSA) and administered by USAID. Initial FSA allocations for environmental projects totaled $35 million, of which EPA was granted approximately one-third, according to Ken Baum, a USAID senior environment policy advisor. Among its many tasks, the research team will look at ways to improve monitoring air pollution levels, the regulatory process, and the role of public participation, as well as make technical recommendations. Successful approaches will be applied to other Russian industrial centers where appropriate.

"We have a whole environmental health strategy that we're evolving," says Michelle Brown, USAID senior environment advisor in Moscow. "Our main objectives are to first reduce the health risks caused by pollution by helping to improve the air quality in Volgograd. Then we will apply that strategy to Russia as a whole."

Still in its genesis, the program included several U.S./Russian trips to factories in Volgograd during 1993 and early 1994. As part of its short-term recommendations, the team will stress low-cost/no-cost control measures that can be put into effect quickly. For example, during a visit to a farm equipment factory, the team suggested changing the nozzles used to spray paint tractor parts in order to reduce organic emissions. In another plant, they determined that a larger hood over an electric arc furnace would greatly improve the capture and conduction of fumes and smoke to an existing emissions control device. Both the new nozzles and hoods can be made in Russia.

"We're hopeful that a lot of short-term improvements can be made using Russian materials and Russian labor because they have the workers available but not the money to purchase equipment from abroad," says Pace. "In the long term, however, they may need to buy specific air pollution control equipment from vendors on the outside."

In October 1993, the team conducted